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Modeling the Use of Triple Combination Therapy in Five Countries: Nevirapine, Zidovudine, and Didanosine

Andrea K. Biddle, PhD,[1] Kit N. Simpson, DrPH[2]

[1]Department of Health Policy and Administration, School of Public Health, University of North Carolina, Chapel Hill, NC;
[2]College of Pharmacy, Medical University of South Carolina, Charleston, SC

ABSTRACT

Objective: In this study, we modify previously published models to estimate the short- and long-term consequences of nevirapine triple combination therapy use in five developed countries. Current pharmacoeconomic practice requires the de novo model development for each new therapy comparison. This approach is lengthy and costly, and it may yield models with very different structures. Standardized, detailed disclosure of model assumptions and parameters makes it possible to recycle published models with minor structural modifications to examine the efficiency of therapies based on new trial data.

Methods: Two well-publicized models of HIV therapy are modified to fit new trial data comparing double and triple combination therapy with nevirapine; model parameters are adjusted to represent clinical practice and cost structure in five countries. A short-term model uses trial data from advanced-stage patients to estimate first-year costs and consequences. A long-term model uses data from antiretroviral-naïve patients to estimate long-term cost-effectiveness.

Results: During the first year, for each 100 individuals treated with nevirapine triple combination therapy, 2.7 deaths and 30.8–31.4 opportunistic disease events would be averted compared to employing dual therapy. Additionally, 61% to 142% of the first-year costs of nevirapine therapy would be offset by other medical care costs savings [FF19,749, DM3,778, 3334 (×1000) lire, 293 (×1000) ptas, and US $3,569]. Compared to dual combination therapy, nevirapine triple combination therapy is predicted to yield incremental cost-effectiveness ratios (discounted at 3%) of FF101,057, DM30,709, 28,066 (×1000) lire, 1294 (×1000) ptas, and US $14,338.

Conclusion: Published, well-constructed, and documented cost-effectiveness models can be reused to estimate the economic impact of therapies for HIV disease. Such models can also be used to provide insight into the factors that affect efficiency across countries. Our use of clinical trial data on nevirapine, together with published HIV economic models, provides support for the hypothesis that nevirapine is cost-effective under the cost structures of five developed countries.

Keywords: Acquired Immunodeficiency Syndrome, anti-HIV agents, combination, cost analysis, cost-benefit analysis, costs, drug therapy, HIV, nevirapine.

Introduction

Currently three classes of antiretroviral drugs are available for the treatment of HIV/AIDS, providing physicians and patients with a number of promising options for the control of the virus. These new combinations of drugs, together with improved monitoring capability, allow the physician to customize drug therapy to reflect the patient's viral load, level of immunosuppression, preferences for treatment, previous drug toxicities, and resistance. Antiretroviral therapies, employed in double or triple combinations, can control viral replication, diminish CD4 cell count depletion, and slow the progression of the disease [1]. However, rapid viral mutation [2,3] results in these therapies being effective only for limited periods until eventually viral replication begins anew. Recent consensus panels recommend that potent combination therapy be employed early in the disease process to reduce the viral load to below the level of quantitation [4,5]. Furthermore, these groups suggest that alternative therapy combinations, dictated by drug interactions, previous therapy, and crossresistance patterns, must be employed and revised as viral breakthrough or development

Address correspondence to: Andrea K. Biddle, PhD, University of North Carolina at Chapel Hill, Department of Health Policy and Administration, CB# 7400, Chapel Hill, NC 27599–7400. E-mail: Andrea_Biddle@unc.edu

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of resistance occurs or as a result of physician judgment or patient preferences.

Recently completed and ongoing clinical trials [6,7] demonstrate that nevirapine in combination with zidovudine (ZDV) and didanosine (ddI) can slow further destruction of the immune system compared with ZDV and ddI dual combination therapy, adding an important new weapon against the human immunodeficiency virus. Extended follow-up of individuals receiving this therapy revealed that more than 64% of those still taking the drug combination after 2 years maintained viral loads below the level of quantitation [8]. These results suggest that nevirapine triple combination therapy may play an important role in the HIV/AIDS therapy sequence.

The cost of care for individuals with HIV/AIDS is high, and resources to pay for this care are increasingly scarce [5]. This is especially true for antiretroviral therapy budgets, because of the large number of effective drugs that have entered the market recently, and because study results indicate that combination therapy is the only effective approach to controlling the virus [4]. Patients, physicians, third-party payers, and governments must look for evidence that new drugs and drug combinations provide good value for money. To assess the value of a new or alternative drug combination, decision-makers balance the maintenance of health and the reduction in costs associated with avoiding hospital admissions and opportunistic disease against increases in drug acquisition costs for new or alternative therapy combinations. This assessment should focus on both the short-term (i.e., first-year costs) and the longer-term (i.e., over the expected lifetime of a cohort of individuals). Although many drug trials have begun to collect costs and resource use (i.e., drugs, clinic visits, hospital admissions) data, this is not yet the norm (or standard practice) and such data are absent for many promising drug combinations. In the absence of these data, it is necessary to combine available clinical trial data with cost-effectiveness models to estimate the added value of new drugs and combinations [9].

Over the past decade, a number of researchers have presented [10–12] or published [13–17] models estimating the health benefits and economic costs associated with HIV drug therapy. These models have examined short-term [12,17] or long-term [10,11,13–16,18] costs and health benefits, but not both. Additionally, only Simpson et al. [15] and Kempel et al. [11] make cross-national comparisons.

These published models provide more than just a valuable contribution to our understanding of the relationship between two or more individual therapies and the economic efficiency of care; they also capture the essence of the health production process for antiretroviral therapy in general. They do this by specifying the known relationship between prognostic indicators (e.g., CD4 cell count or viral load) and health outcomes (i.e., events or death) based on population data. In addition, they estimate the cost of care provided for a well-described patient group under specific conditions (e.g., for a country or for a provider system within a country). The practice in the field of health economics has been to develop a model de novo for each therapy comparison. However, this approach is lengthy and costly, and it has the disadvantage that the model structures often vary across studies. The move toward standardized, detailed disclosure of model assumptions and parameters makes it possible to recycle some published models with only minor structural modifications to examine the efficiency of therapies based on new trial data.

The objective of this study was to compare nevirapine triple combination therapy to dual combination therapy in five developed countries. We take two well-publicized models [15,16], modify them to fit the new trial data (i.e., data from each of two clinical trials), and adjust the model parameters to represent the clinical practice and medical care cost structures in these countries. The strength of this approach is that it is frugal, avoids inserting the author's biases into the model's structure, and allows parsimonious descriptions of models that are quite complex. The weaknesses of the approach are that the therapeutic effects evidenced in the trial reports may not be captured with sufficient fidelity because the models were not designed specifically for these trials, and that the modifications to the model parameters made may run counter to unspecified structural assumptions embedded in the original models.

Methods

Country-specific differences in disease epidemiology, treatment patterns, and resource utilization indicate that it is important to assess a new or alternative therapy within the country-specific environment to determine its potential value or contribution in that location. Additionally, assessments of the same therapy in several countries provide evidence of the extent to which a therapy can add

value, to different degrees, depending upon country-specific parameters.

Here, two modeling approaches (each used with one specific set of trial data) are used to predict the short- and long-term economic performance of nevirapine triple combination therapy in five countries—France, Germany, Italy, Spain, and the United States. The first model uses data from a trial of advanced-stage patients to estimate the first-year drug acquisition costs compared with the reduction in healthcare costs (e.g., costs of hospitalization, clinic visits, specialist consults) associated with opportunistic disease events averted. The second model uses trial data from antiretroviral-naïve patients to estimate the lifetime cost-effectiveness of nevirapine triple combination therapy, compared with dual therapy without nevirapine, assuming subsequent treatment with protease inhibitor combinations.

Modeling the First-Year Health Benefits and Costs of Nevirapine Triple Therapy

Model Description and Structure. The Simpson et al. [15] model was modified to evaluate the first-year impact of using nevirapine triple combination therapy compared to dual drug therapy. The original model was specifically designed to accommodate local epidemiological patterns and variations in AIDS clinical practice patterns in North America and several European countries. In the current application, this model is well suited for three reasons:

1. It is possible to adjust for differences in the environmentally related risk of specific opportunistic disease events (ODEs; e.g., rate of positive titer for toxoplasmosis) by comparing the model's base incidence assumptions for ODEs to the epidemiological reports for a particular country.
2. By changing treatment algorithms to reflect a prespecified set of treatment patterns for acute and chronic clinical events until they reflect those of a specific country, it is possible to adjust for country-specific treatment practices.
3. Country-specific input price differences are reflected by using unit cost values for a large set of key cost drivers in HIV management (e.g., drugs, visits, hospital costs) that best reflect current opportunity cost.

Simpson et al. [15] use a Markov process to link disease stage, as measured by level of immunosuppression, to risk of opportunistic disease events (Fig. 1). Opportunistic disease events are subsequently linked to resource use (e.g., diagnostic tests, drugs, clinic visits, specialist consults, hospitalization days) and cost. In the first stage of the model, a patient cohort is classified into six mutually exclusive opportunistic disease event risk categories by level of immune suppression (as measured by CD4 cell count in cells/mm^3)—$<$50, 50–99, 100–149, 150–199, 200–299, and $\geqslant$300. Risk is measured by the geometric mean of the CD4 cell decline curve for a 60-day period from appropriate clinical trial data. Eight vectors of ODE probability density estimates, derived from published epidemiological data fitting these risk groups, are used to estimate the expected number of HIV-related events per year. These event groups—Pneumocystis carinii pneumonia, toxoplasmic encephalitis, Mycobacterium avium complex, cryptococcal meningitis, severe Kaposi's sarcoma, cytomegalovirus (CMV) retinitis, lymphoma, and tuberculosis—are those most frequently seen in AIDS.

To assign resource use and costs to the annual estimates of ODEs, a set of standard treatment algorithms was adjusted in the original model development by Simpson et al. [15] by experienced physicians to reflect the local practice patterns in each of the five countries. Country-specific input prices for diagnostic tests, drugs, clinic visits, specialist consults, hospital ward days, intensive care unit (ICU) days, diagnostic procedures, and curative/palliative procedures were combined with the treatment algorithms to derive the average costs of care for each ODE. Simpson et al. [15] provide additional information concerning the modeling, treatment algorithm development, and cost estimation processes.

To use the nevirapine clinical trial data several modifications of the Simpson et al. [15] model were required. First, the model was truncated after 1 year; instead of extrapolating long-term survival, the model was used to predict only events and costs for the first year of therapy. Simpson and LaVallee [12] performed a similar model truncation to describe the first-year impact of saquinavir triple combination therapy. The model described here reports treatment impacts in terms of annual ODEs and deaths and costs of medical care. Second, ODEs were expanded to capture more comprehensively the spectrum of AIDS-related disease, allowing for the inclusion of such conditions as bacterial pneumonia, wasting syndrome, AIDS dementia, and nonspecific infections. The ODEs included in the modified model are 1) Pneumocystis carinii pneumonia; 2) toxoplasmic encephalitis; 3)

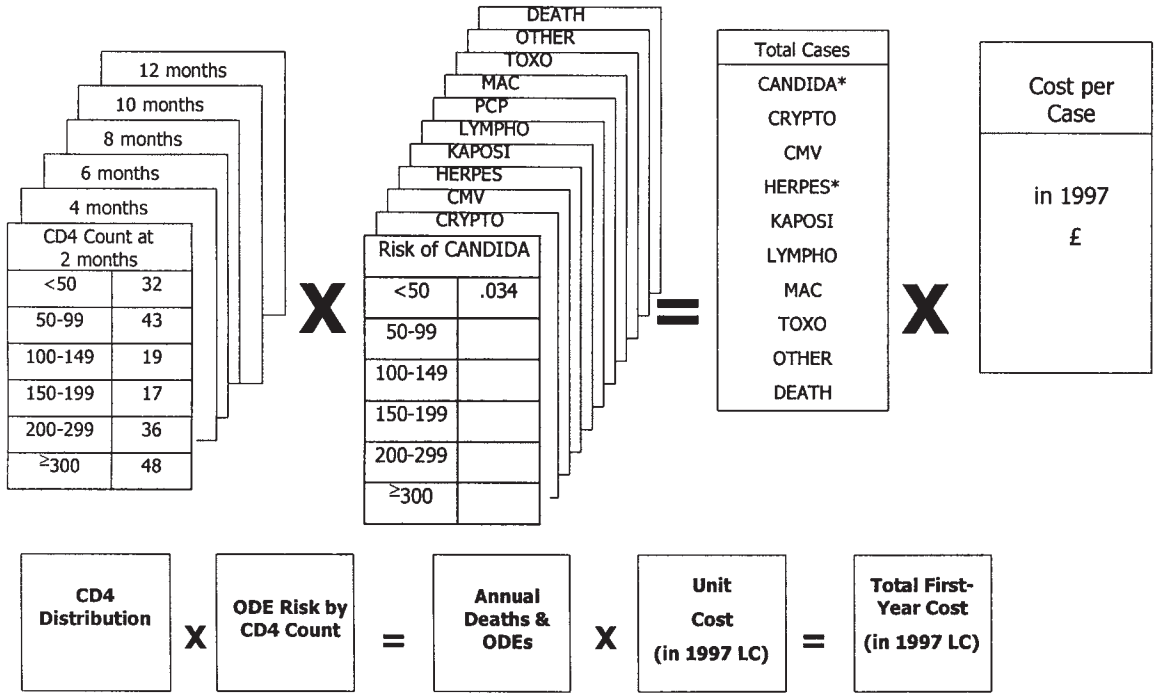

Figure 1 This figure provides a schematic representation of the Simpson et al. [15] model. Modifications required for use with the ACTG 241 clinical trial data are indicated by an asterisk. PCP, Pneumocystis carinii pneumonia; MAC, Mycobacterium avium complex; KAPOSI, Kaposi's sarcoma; CRYPTO, cryptococcal meningitis; CMV, cytomegalovirus retinitis and other CMV disease; LYMPHO, central nervous system and non-Hodgkin's lymphoma; HERPES, chronic herpes simplex virus infection; CANDIDA, Candida esophagitis; TOXO, toxoplasmosis meningitis; OTHER, other acute events (rehydration for wasting syndrome or cryptosporidiosis, neurologic workup for HIV encephalopathy, bacterial pneumonia, severe/multi-drug-resistant tuberculosis, terminal care); ODE, opportunistic disease event; LC, local currency (French francs, German deutschemarks, Italian lire, Spanish pesetas, United States dollars).

Mycobacterium avium complex; 4) cryptococcal meningitis; 5) cytomegalovirus (CMV) retinitis and other CMV disease; 6) central nervous system lymphoma and non-Hodgkin's lymphoma; 7) severe Kaposi's sarcoma; 8) chronic Herpes simplex virus infection; 9) Candida esophagitis; and 10) other acute events (rehydration for wasting syndrome, cryptosporidiosis, neurological workup for HIV encephalopathy, bacterial pneumonia, severe/multi-drug-resistant tuberculosis, terminal care).

During the period of 1 year, the modified model follows two hypothetical cohorts of 100 patients who receive either nevirapine triple combination therapy or ZDV/ddI dual therapy. Annual ODEs and deaths are estimated during the modeling process by simulating the risk of developing 1 of the 10 specific events during each of six 2-month cycles. During a 2-month cycle, individuals remain well, die, or experience one of the events. Individuals who remain well during a cycle begin the subsequent model cycle in the risk category that matches their CD4 cell counts at the beginning of that cycle. At the end of the year, the expected number of ODEs, deaths, and costs are summed across the cycles to obtain annual estimates for both the triple and dual therapy treatment arms.

Data Sources. The input parameters for the model are presented in Tables 1 and 2. From a short-term economic perspective, it is necessary to model a population that is broadly representative of the entire HIV disease population in each of the five countries. The population of the AIDS Clinical Trial Group (ACTG) 241 trial, adults with HIV infection who had CD4 cell counts of $\leqslant$350 cells/mm^3 and who had at least 6 months of prior treatment with nucleoside reverse transcriptase inhibitors [6], is quite representative of patients likely to be treated with nevirapine triple combination therapy in the countries of interest. The 2-month risk of ODEs and death were estimated from the 52-week CD4 cell count data from ACTG 241 [6] (Table 1).

The CD4 cell count distribution was estimated for each 2-month period; when two or more measurements were reported for a 2-month period, the

Table 1 Baseline CD4 cell counts and risks of opportunistic disease events and death for the short-term model of nevirapine triple combination therapy, by country, 1997

Model parameter	Value			Source
Baseline CD4 cell count (cells/mm^3) (%)	ZDV + ddI		NVP + ZDV + ddI	[6]
<50	25.4		21.3	
50–99	13.4		12.7	
100–149	13.4		18.8	
150–199	11.4		9.1	
200–299	25.9		26.9	
Annual risk of opportunistic disease events and death (%)*	France/Germany	Italy/Spain	United States	[12,15,20]
Pneumocystis carinii pneumonia	12.8	12.8	12.8	
Mycobacterium avium complex	14.8	14.8	18.0	
Kaposi's sarcoma	15.1	15.1	15.1	
Cryptococcal meningitis	1.4	1.4	1.4	
Cytomegalovirus (CMV) retinitis and other CMV disease	25.5	25.5	25.5	
Candida esophagitis	9.9	9.9	9.9	
Chronic Herpes simplex virus infection	35.3	35.3	35.3	
Lymphoma	2.4	2.4	2.4	
Toxoplasmic encephalitis	2.4	4.8	2.4	
Other events	40.0	40.0	40.0	
Death by CD4 count (cells/mm^3) (%)				
<50	22.6			[21]
50–99	11.9			
100–149	6.0			
150–199	1.8			

*Totals may not add to 100.0% because of rounding.
ddI, didanosine; NVP, nevirapine; ZDV, zidovudine.

mean CD4 cell count was calculated and subsequently used to obtain the distribution. Preliminary analyses revealed a predicted maldistribution of economic costs between the two treatment arms resulting from slight imbalances in the baseline distribution of patients with very low CD4 cell counts. This imbalance, though not representing clinical bias, results in the overrepresentation of the risk of high-cost ODEs. Indirect adjustment techniques [19] were required to quantify and to equalize the economic bias at baseline between the two treatment arms. First, the results for the dual

Table 2 Costs of opportunistic disease events in 1997, by country

			Italy (×1000 lire)‡			
Opportunistic disease event	France (FF)*	Germany (DM)†	Base case	Spanish rates	Spain (ptas)†	US (US$)§
Pneumocystis carinii pneumonia	76,485	4,566	8,846	11,146	878,499	8,481
Mycobacterium avium complex	99,499	21,692	20,417	36,546	1,909,387	8,738
Kaposi's sarcoma	64,729	2,712	3,561	3,309	347,991	5,400
Cryptococcal meningitis	105,170	23,166	36,665	31,072	2,249,207	16,988
Cytomegalovirus retinitis	106,271	56,942	37,688	42,964	3,288,098	51,987
Candida esophagitis	59,342	526	926	584	445,448	1,495
Herpes	59,342‖	1,603	781	1,484	221,107	437
Lymphoma	83,789	21,468	23,546	20,022	2,001,722	13,197
Toxoplasmic encephalitis	76,875	24,434	12,131	7,620	1,834,551	14,483
Other events	76,485	4,566	8,846	7,977	571,273	8,217

*Simpson and LaVallee [12].
†Kempel et al. [22].
‡Base case uses Italian DRG costs as inputs to the cost algorithms of Simpson and LaVallee [12]. These cost algorithms were modified to reflect admissions rates identical to those reported in Spain.
§Brown et al. [23].
‖The cost of herpes is not reported by Kempel et al. [23]. Because the treatment for herpes and candidiasis are similar, the costs of care for herpes are assumed to be identical to those for Candida esophagitis.
Cost figures reported in 1997 local currency. Cost figures were inflated using the country-specific All-Items Consumer Price Index reported by the Organization for Economic Cooperation and Development Main Economic Indicators [39] or, in the case of the United States, the Medical Care Component of the Consumer Price Index [40].
Cytomegalovirus retinitis, Cytomegalovirus (CMV) retinitis and other CMV disease; Herpes, chronic Herpes simplex virus infection; Lymphoma, central nervous system lymphoma and non-Hodgkin's lymphoma; Other events, other acute events (rehydration for wasting syndrome or cryptosporidiosis, neurologic workup for HIV encephalopathy, bacterial pneumonia, severe/multi-drug-resistant tuberculosis, terminal care); FF, French francs; DM, German deutschemarks; lire, Italian lire; ptas, Spanish pesetas; US$, United States dollars.

therapy arm were estimated separately for patients in each of the model's risk strata (based on their baseline CD4 values). Next, using the baseline CD4 cell count distribution of the patients in the nevirapine triple therapy arm as weights, the weighted means for all events (ODEs and deaths) and costs were calculated. However, this approach increases the risk of redistributing unknown biasing factors while removing the known bias that occurred during randomization. Consequently, both unadjusted and adjusted results are reported.

The risks of ODEs and death (Table 1) were estimated using four data sources [12,15,20,21]. The country-specific risks of ODEs estimated by Simpson et al. [15] were employed for the French, German, Italian, and American models. Spain was not included in the original Simpson et al. [15] model; therefore, risk data were derived from the later Simpson and LaVallee [12] model. To reflect epidemiological differences between the five countries, the incidence rates for toxoplasmic encephalitis and Mycobacterium avium complex were adjusted using the data of Bacellar et al. [20]. The risk of death is based on a survival analysis of 289 men with CD4 cell counts $\leq$100 cells/mm^3 [21]. For each of the five countries, the risk of "other events" is based on the clinical judgments of the physician consultants used in Simpson and LaVallee's [12] model of the effect of saquinavir triple combination therapy.

The cost perspective from the original model [15] was retained. This model estimates the combined factor costs to all payers—whether these direct medical care costs are paid by an insurer, a health authority, or the patient, or absorbed as bad debt by a provider. Standard cost estimates for the treatment of ODEs were derived from three sources [12,22,23]. These data do not reflect the health system reforms undertaken in Italy since late 1995, and it was necessary to reestimate treatment costs using available diagnosis-related group (DRG) costs (personal communication, Boehringer Ingelheim Italia s.p.a., January 1998). However, because the Italian DRGs do not correspond directly to all of the ODEs used in the current model, and because, in some cases, the DRGs may include conditions that are not always AIDS related, the costs reported may yet underestimate the actual costs of providing care. To address this issue, an alternative set of cost estimates was developed by assuming that disease epidemiology and treatment patterns are similar in Italy and Spain. To estimate these alternative costs, the Italian care algorithms and unit costs developed by Simpson and LaVallee [12] were modified to incorporate Spanish hospital admission rates for each of the ODEs. The impact of these alternative costs is tested using sensitivity analysis. The country-specific costs are reported in Table 2. The daily dosage of two 200-mg nevirapine tablets is assumed to be identical across the five countries. Per-tablet prices were obtained from Boehringer Ingelheim GmbH (personal communication, 12 December 1997). Daily costs of nevirapine are US$6.88, FF49, DM12.85, 15,000 lire, and 1089.15 ptas.

Modeling the Long-Term Cost-Effectiveness of Nevirapine Triple Combination Therapy

The model published by Chancellor et al. [16] was modified to estimate the long-term health benefits and economic costs of adding nevirapine to ZDV/ddI dual combination therapy. As originally formulated, the Chancellor et al. [16] model employs a Markov process that follows a patient cohort as it progresses through four health states—CD4 cell count $\geq$200 and $<$500 cells/mm^3 and no AIDS (High CD4), CD4 $<$200 cells/mm^3 and no AIDS (Low CD4), AIDS, and death (Fig. 2). The modification of the model that was employed was required to 1) more closely model recommended treatment practices; and 2) accommodate available nevirapine clinical trial data.

In actual clinical practice, and according to current treatment recommendations [4,5], patients are switched to subsequent therapies as viral breakthrough or development of resistance occurs or as a result of physician judgment or patient preference. The structure of the Chancellor et al. [16] model assumes no therapy revision over the model's duration. The modified model is structured to reflect clinical practice and recommendations by assuming that drug therapy is revised as viral breakthrough occurs. Subsequent to viral breakthrough, nevirapine triple combination therapy or ZDV/ddI dual combination therapy is replaced in succession by one of two sequences of a protease inhibitor combined with two nucleoside reverse transcriptase inhibitors.

The Chancellor et al. [16] model captured treatment differences by using the risk ratio from a meta-analysis of specific clinical events observed for patients in a group of clinical trials to adjust transition probabilities between the health states. The available nevirapine clinical trial data could not be employed in this way because many nevirapine trials have only reported surrogate marker results to date. In the model presented here, surro-

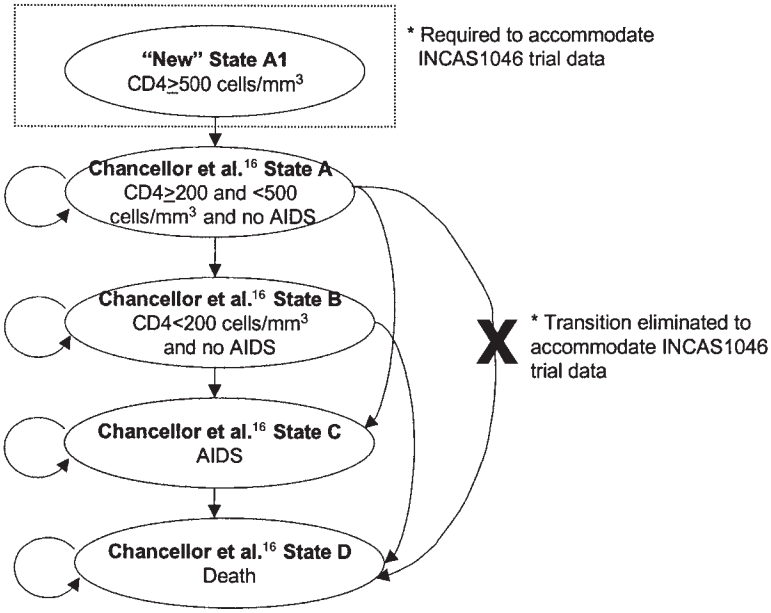

Figure 2 This figure provides a schematic representation of the Chancellor et al. [16] model indicating modifications required by the INCAS 1046 trial data. The dashed box indicates a new health state that was added to accommodate the data; the X indicates a state transition that was eliminated as a result of the available nevirapine trial data.

gate marker responses, as measured by 4- to 8-week mean CD4 cell increases and mean time for return of CD4 cell count to baseline, were employed to capture the difference in risk of progression between the two treatments. The transition probabilities between the health states in the model were reduced by this difference in risk. To accommodate the nevirapine trial data for patients in the early stages of HIV infection, it was necessary to add a fifth health state, CD4 $\geqslant$ 500, to capture the small number of patients whose 4- to 6-week CD4 cell increase would move them beyond the 500 cells/mm^3 upper boundary of the Chancellor et al. [16] High CD4 health state. Also required was a one-time transition into this state from the High CD4 state (and a corresponding shift from the Low CD4 state to the High CD4 state). The transition from the CD4 $\geqslant$ 500 state back to the High CD4 state captured the median time at which patients return to baseline as reported in the trials.

As currently structured the modeling process follows two cohorts of 100 individuals for about 15 years (15 1-year cycles), or until 75% of the cohort members have died. Although Chancellor et al. [16] employ a 20-year time horizon, a shorter period has been selected to reflect a more realistic time horizon for survival therapy decision-making. One group receives triple combination therapy with nevirapine, ZDV, and ddI; the other receives dual combination therapy of ZDV and ddI. The total life expectancy for the treatment cohorts is calculated by summing the expected number of years spent in each of the four living health states. The expected number of years spent in a particular health state is calculated by summing the total number of person-years spent in a particular health state and dividing by the cohort size. The expected total costs for each treatment is calculated by multiplying the number of years that patients spend in each of the four living states by the health-state-specific care costs. The incremental cost-effectiveness ratio (reported in local currency per year of life saved) is calculated by dividing the total cost difference (i.e., medical care and antiretroviral drug costs) by the difference in survival.

Data Sources. Treatment effect duration data are provided in Table 3. INCAS 1046 trial data were used to derive the treatment effects and duration for the nevirapine triple combination and ZDV/ddI dual combination therapies [7]. This population of AIDS-free, antiretroviral-therapy-naïve adults (CD4 cell count range: 200–600 cells/mm^3) was selected because it best reflects current recommendations for early initiation of antiretroviral therapy [4,5]. The annual transition probabilities from the Chancellor et al. [16] model were modified as follows. To account for the 100-cell/mm^3 increase that is expected to result from nevirapine triple combination therapy (52-week INCAS 1046 data) [7], a proportion of the upper 50% of individuals in the Low CD4 and High CD4 cell states is assumed to progress upward into the next highest categories—High CD4 and CD4 $\geqslant$ 500, respectively. For example, a 100-cell increase would

Table 3 Input parameters for the lifetime cost-effectiveness model, 1997

Model parameter	Value		Source
Estimated duration of effect (in months)			
ZDV + ddI	15		[7]
NVP + ZDV + ddI	24		[7]
First protease inhibitor combination	18		[25–28]
Second protease inhibitor combination	15		[30–34]
Weighting* factors (%)	US/ France	Germany/ Italy/Spain	
Protease inhibitors			[34]
Indinavir	30	33.3	
Nelfinavir	30	—†	
Ritonavir	20	33.3	
Saquinavir	20	33.3	
NRTIs			[4,32,35,36]
Zidovudine	25		
Lamivudine	20		
Didanosine	25		
Zalcitabine	15		
Stavudine	10		

*The weights reflect the proportion of use, and they are combined with country-specific costs to derive the costs of the protease inhibitor combinations.
†At the time of model development, nelfinavir was not licensed for sale in Germany, Italy, or Spain. Equal weighting used to derive the cost of the protease inhibitor combination.
ddI, didanosine; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; ZDV, zidovudine.

move those with CD4 cell counts $\geq$100 but $<$200 cells/mm^3 (i.e., Low CD4) into the High CD4 cell category; a similar increase would move those High CD4 individuals with CD4 counts of 400 cells/mm^3 and higher into the CD4 $\geq$ 500 category. For individuals in the CD4 $\geq$ 500 health state, the transition probability back to the High CD4 state is assumed to be 50% lower during the subsequent model cycle [24]. The CD4 cell increase is assumed to occur during the first quarter and to slowly decline, returning to baseline within the time frame indicated in the trial data. A similar approach was taken for the comparison arm but the transition back to baseline was assumed to be faster. This may bias our estimates slightly against nevirapine.

Median time to viral breakthrough subsequent to nevirapine triple therapy and ZDV/ddI dual therapy are assumed to be 24 months and 15 months, respectively, after therapy initiation [7]. The model assumes a 100-cell increase in CD4 cell count and that viral breakthrough occurs at 18 months for the first protease inhibitor combination. Clinical trials evaluating the duration of viral suppression for protease inhibitors are ongoing with only preliminary results available [25–28]. However, the results of one trial indicates that at 100 weeks, 69% of individuals receiving triple therapy with indinavir, lamivudine, and zidovudine had viral levels measuring $<$50 copies per ml [26]. This suggests that 18-month assumption may be somewhat conservative. Because recent clinical trials [29–33] suggest that viral breakthrough for subsequent protease inhibitor combinations occurs earlier and results in less of a CD4 cell count increase in protease-inhibitor-experienced individuals, viral breakthrough for the second combination is assumed to occur at 15 months with a CD4 cell response seen only in 90% of patients.

Each of the two protease inhibitor combinations used after initial viral breakthrough includes one protease inhibitor and two nucleoside reverse transcriptase inhibitors. These combinations compose a composite of the existing protease inhibitor combinations, reflecting the proportion of use of highly active antiretroviral therapy (HAART) therapies currently recommended in centers of excellence [34]. The nucleoside reverse transcriptase inhibitor mix is derived by weighting the proportion of use and length of time of expected use for each combination, given what is currently understood about patterns of overlapping resistance [4,32,35,36].

Like the original Chancellor et al. [16] model, the long-term cost-effectiveness model employs the perspective of the healthcare system to enumerate costs. Country-specific health state and drug therapy costs are presented in Table 4. Because the Chancellor et al. [16] health-state-specific cost data are available only for the United Kingdom, it was necessary to calculate an AIDS-specific cost conversion factor to translate costs for each of the five country-specific models described here. To maintain consistency in cost estimation between the two models, we used data from the short-term model described earlier for this calculation. This conversion factor was calculated by dividing the weighted cost of care for AIDS events in each of the five countries by the average weighted cost of care for patients in the United Kingdom reported by Simpson and LaVallee [12]. The United Kingdom health-state-specific cost data reported by Chancellor et al. [16] then were multiplied by these AIDS-specific conversion factors, producing estimates (in local currency) of the country-specific cost of care for each health state.

The costs of the protease inhibitor combinations are a weighted average of the country-specific ex-factory prices of these combinations (personal communication, Boehringer Ingleheim, January–

Table 4 Annual drug and health-state costs (1997 values) used in the long-term cost-effectiveness models, by country

	Average annual costs (in local currency)					
			Italy (×1000 lire)			
Type of cost	France (FF)	Germany (DM)	Base case	Spanish rates	Spain (Ptas)	US (US$)
Annual drug therapy costs*						
ZDV + ddI	27,203	8,549	5,809	—	675,812	5,753
NVP + ZDV + ddI	45,088	16,240	11,284	—	1,073,352	8,264
Protease inhibitor + 2 NRTIs‡	47,232	17,332	12,562	—	2,582,936	11,504
Annual health state costs†						
CD4 ⩾500 cells/mm³	7,906	2,336	2,546	3,050	196,328	1,570
High CD4: CD4 ⩾200 and <500 cells/mm³	15,812	4,672	5,092	6,100	392,656	3,140
Low CD4: CD4 <200 cells/mm³	26,348	7,780	8,484	10,165	654,256	5,232
AIDS	89,576	26,456	28,844	34,559	2,224,368	17,784

*Because nevirapine was not yet marketed in the four European countries, ex-factory prices (obtained from Boehringer Ingelheim operating units in each country) were employed. For the United States, prices were derived from the 1997 U.S. Red Book [37].
†Costs were derived from Chancellor et al. [16] as described in the Methods section.
‡Weighted combination of the costs of existing protease inhibitor triple combination therapies.
Cost figures reported in 1997 local currency. Cost figures were inflated using the country-specific All-Items Consumer Price Index reported by the Organization for Economic Cooperation and Development Main Economic Indicators [39], or in the case of the United States, the Medical Care Component of the Consumer Price Index [40].
ddI, didanosine; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; ZDV, zidovudine.

February 1998). Ex-factory prices were used for the four European countries because nevirapine was not yet licensed at the time of the development of this model. In the US model, average wholesale prices, derived from the US Red Book [37], were used for all drugs except nelfinavir. Because nelfinavir was not approved for use at the time of the 1997 Red Book's [37] publication, the price given at the time of FDA approval was used [38]. The daily dosage for nevirapine is two 200-mg tablets with daily costs of US$6.88, FF49, DM12.85, 15,000 lire, and 1089.15 ptas.

To ensure comparability across the five countries, all costs were standardized to the second quarter of 1997, using the country-specific All-Items Consumer Price Index [39]. (More current figures were not available for all five countries at the time of model development.) The Medical Care Component of the Consumer Price Index [40] was used for the American model. Estimates are presented in the local currency of each country. SAS statistical analysis software, versions 6.11/6.12 (SAS Institute, Cary, NC), was employed to analyze all clinical trial data. Excel spreadsheet software (Microsoft Corporation, Redmond, WA) was used to estimate the results for the two models.

Sensitivity Analyses

Economic models, including cost-effectiveness models, by their nature provide estimates that incorporate uncertainty about the true costs and clinical effectiveness and uncertainty about the model structure [41]. Sensitivity analysis provides a systematic evaluation of the effects of these uncertainties. In the present analysis, the robustness of the models to the structural modifications made and the country-specific parameters used is assessed with a series of sensitivity analyses similar to those employed by Chancellor et al. [16]. For each of the five countries, sensitivity analyses were conducted on three key parameters—timing of therapy initiation, duration of therapy, and discount rate.

Despite the recommendation that antiretroviral therapy be initiated before significant immunosuppression occurs [4,5], it is important to understand the potential effect of beginning therapy at different stages of the disease. Some physicians may prescribe nevirapine triple combination therapy for individuals with significant immunosuppression, while others may prescribe this therapy for those who have received antiretroviral therapy previously. The effects on costs and outcomes of beginning treatment in individuals with significant damage to the immune system and as a rescue therapy (i.e., therapy when other treatments have failed) were estimated, beginning the entire patient cohort in the low CD4 and AIDS health states. To evaluate the model's sensitivity to the duration of the effect of nevirapine, two alternative scenarios—a more optimistic scenario of 30 months [8] and a more pessimistic one using 15 months—were employed.

Because policy-makers vary in how they value costs and outcomes that occur in the present compared to those that accrue in the future, it is necessary to adjust the results of the model using a dis-

count rate. However, disagreement persists about whether it is appropriate to discount both costs and outcomes (in this case, years of life saved) [42,43] and which discount rate to use [43]. In the base case, both costs and outcomes that occur after the first year are discounted at 3% per annum. Alternatively, the model was reestimated using no discount rate for either costs or outcomes and by discounting both costs and outcomes by 1%, 5%, and 7% per annum as recommended by Lipscomb et al. [43].

Because the Italian healthcare system currently is undergoing major healthcare reforms, and even with the incorporation of the Italian DRG costs provided by Boehringer Ingelheim Italia s.p.a. (January 1998), the care algorithms and unit costs derived earlier by Simpson and LaVallee [12] may underestimate the current costs of HIV/AIDS care in Italy. Consequently, the Italian model was reestimated using a set of cost estimates based on HIV/AIDS hospital admission rates in Spain, a country generally believed to have disease epidemiology and treatment practices similar to those observed in Italy.

Results

The Impact of Adding Nevirapine to ZDV/ddI Dual Therapy in the Short Term

The burden of opportunistic disease and death is greater for dual combination therapy than for triple combination therapy with nevirapine (Table 5). Treatment with triple combination therapy would prevent 28.5% of opportunistic disease events and 20.5% of deaths compared to dual therapy. A reduction in the projected cost of care (e.g., hospitalization, clinic visits, drugs), exclusive of the cost of nevirapine, accompanies this improvement in survival and reduction in disease burden. For the first year, the projected savings in medical care costs represent cost-offsets of 75.2% (Italian base case) to 175.5% (United States) of the annual cost of treatment with nevirapine (Table 6) for a group of patients similar to those enrolled in the ACTG 241 trial. After adjustment for economic bias in the ACTG 241 baseline data, the use of nevirapine triple therapy would be expected to result in 23.1% and 18.3% fewer opportunistic disease events and deaths, respectively. Projected cost-offsets then would range from 60.9% (Italian base case) to 142.1% (United States).

Base case costs likely underestimate the current costs of HIV/AIDS care in Italy, given the ongoing healthcare system reforms; however, more recent unit costs were not available at the time of model development. Consequently, the model was reestimated assuming that admission rates in Italy would be similar to those observed in Spain, where the healthcare system faces comparable disease epidemiology and has similar treatment patterns. Under this new scenario, medical care savings increase to 4823 (×1000) lire per patient, representing 88.1% of the annual total cost of treatment with nevirapine. After adjusting for the economic bias present in the ACTG 241 data, projected costs savings would be expected to decline to 3907 (×1000) lire per patient, representing an offset of 71.4% of the nevirapine treatment cost.

Long-Term Cost-Effectiveness of Nevirapine Triple Combination Therapy

Total costs, survival, and incremental cost-effectiveness ratios (reported in local currency and US dollars per life-year saved) for each country are reported in Table 7. Under base case assumptions, 100 individuals initially treated with nevirapine triple combination therapy would be expected to survive for a total of 1050 years, a cumulative survival increase of 42.4 years compared to ZDV/ddI dual therapy. The cost in US dollars per life-year ranges from $8,831 (Spain) to $17,702 (Germany) per additional life-year saved (1997 average currency conversion rates—1.73 DM = US$1; 146.36 ptas = US$1; 5.84 FF = US$1; 1703 lire = US$1) [44]. These ratios all are less than the US$50,000 per life-year saved (or per quality-adjusted life-

Table 5 Number of opportunistic diseases events and deaths for a 100-person cohort* receiving dual and triple combination therapy

	France/Germany		Italy/Spain		United States	
Outcomes	Dual	Triple	Dual	Triple	Dual	Triple
Opportunistic disease events	107.8	77.0	109.5	78.3	110.1	78.7
Deaths	13.1	10.4	13.1	10.4	13.1	10.4

*The cohort includes 100 HIV-infected adults who had CD4 cell counts of ⩽350 cells/mm^3 and who had at least 6 months of prior treatment with nucleoside reverse transcriptase inhibitors.
Dual, zidovudine/didanosine dual therapy; Triple, nevirapine/zidovudine/didanosine triple therapy.

Table 6 Projected 1-year treatment costs and cost-offsets in 1997 local currency, by country

Country	NVP cost/year (in LC)*	Medical care savings (in LC)†		% offset‡	
		Unadjusted	Adjusted§	Unadjusted	Adjusted§
France (FF)	17,885	24,381	19,749	136.3	110.4
Germany (DM)	4,691	4,664	3,778	99.4	80.5
Italy (×1000 lire)					
Base case	5,475	4,116	3,334	75.2	60.9
Spanish rates	5,475	4,823	3,907	88.1	71.4
Spain (×1000 ptas)	398	362	293	91.0	73.7
United States (US$)	2,511	4,406	3,569	175.5	142.1

*Cost per year calculated as the country-specific price per day multiplied by 365 days.
†Projected 1-year cost savings per patient attributable to nevirapine triple combination therapy.
‡Proportion of treatment costs offset by the use of nevirapine triple combination therapy (calculated as the medical care savings divided by the 1-year costs of therapy with nevirapine).
§Adjusted for the economic bias at baseline (ACTG 241) [6].
NVP, nevirapine; LC, local currency; DM, German Deutschemarks; FF, French francs; lire, Italian lire; ptas, Spanish pesetas; US$, United States dollars.

year saved) value that the field has come to assume as an appropriate cost-effectiveness criterion for developed countries.

Subjecting the five country-specific models to a battery of sensitivity analyses reveals patterns similar to those presented by Chancellor et al. [16] (Table 8). The models were most sensitive to the timing of therapy initiation and therapy duration. With the exception of the Spanish model, scenarios in which therapy was begun at a later stage (i.e., all individuals in either the low CD4 health state or with AIDS) yielded substantially higher cost-effectiveness ratios; these ratios, ranging from US$60,779 in Germany to US$66,549 in Italy, slightly exceed the threshold of US$50,000 per life-year saved. In the Spanish model, nevirapine triple therapy was dominant, resulting in better survival at a slightly lower cost than dual combination therapy when therapy was begun in individuals having <200 CD4 cells/mm^3. These findings provide an economic rationale to reinforce the recommendation that antiretroviral therapy should begin before substantial immunocompromise occurs [4,5]. Shortening or lengthening the duration of the effect of nevirapine triple combination therapy resulted in moderate changes in the model results. Reducing the mean duration of effect to 18 months yielded higher incremental cost-effectiveness ratios in each of the five countries, while increasing the duration by a half year (to 30 months) resulted in lower ratios. Employing the health-related quality-of-life adjustments developed by Freedberg et al. [45], the incremental cost-effectiveness ratios become slightly higher; in the US base case, the ratio is US$15,012. If the cost of HAART (of which the nevirapine triple combination therapy is one regimen) increases to more than US$36,000 per year (i.e., the annual cost more than quadruples), the triple combination therapy is no longer cost-effective, assuming a threshold of US$50,000 per life-year saved.

The Italian model demonstrated little sensitivity to cost estimates based on Spanish admission patterns. Only a slight increase from 28,066 (×1000) lire per life-year saved to 28,391 (×1000) lire per life-year saved was predicted. Two patterns of sensitivity were observed when costs and benefits were discounted at 0%, 1%, 5%, and 7%; the base case scenario discounts both at 3% [43]. For Spain and the United States, the incremental cost-

Table 7 Base case* costs, survival, and incremental cost-effectiveness ratios comparing nevirapine triple combination therapy to zidovudine/didanosine dual therapy, by country

Country/therapy	Costs	Survival	Incremental cost-effectiveness ratio	
			LC/LY†	US$/LY‡
France				
Dual therapy	77,041,857	1,007.8		
Triple therapy	81,326,501	1,050.2	101,057	17,306
Germany				
Dual therapy	26,179,948	1,007.8		
Triple therapy	27,481,966	1,050.2	30,709	17,702
Italy				
Dual therapy	22,102,242	1,007.8		
Triple therapy	23,292,195	1,050.2	28,066§	16,472
Spain				
Dual therapy	3,159,084	1,007.8		
Triple therapy	3,213,959	1,050.2	1,294§	8,831
United States				
Dual therapy	17,218,891	1,007.8		
Triple therapy	17,826,815	1,050.2	14,338	—

*Base case scenario as described in Methods section.
†Incremental cost-effectiveness ratios are reported as local currency (LC) per life-year (LY) saved. All costs are reported in 1997 currency values.
‡Incremental cost-effectiveness ratios are reported as United States dollars (US$) per life-year (LY) saved. Currency exchange rates for 1997 are as follows: 1.73 DM = US$1; 146.36 ptas = US$1; 5.84 FF = US$1; 1,703 lire = US$1 [44].
§Italian and Spanish ratios are reported ×1000 lire/life-year and ×1000 ptas/life-year, respectively.

Table 8 Incremental cost-effectiveness ratios of nevirapine triple therapy compared with zidovudine/didanosine therapy: sensitivity analysis results, by country

	Incremental cost-effectiveness ratios (in LC/LY)				
Scenario	France	Germany	Italy*	Spain*	United States
Spanish admission rates†	—	—	28,397	—	—
Time of therapy initiation‡					
All with low CD4	386,155	105,147	113,333	Dominated§	41,747
All with AIDS	219,246	57,175	68,248	1,634	28,182
Duration of nevirapine therapy‖					
18 months	125,156	37,729	36,136	3,251	20,886
30 months	76,263	23,980	20,330	596	10,272
Discount rate					
0%	94,542	29,357	26,506	1,888	15,349
1%	96,305	29,831	26,911	1,702	15,001
5%	107,687	32,038	29,753	836	3,740
7%	116,498	33,894	32,061	324	13,232

*Italian and Spanish ratios are reported ×1000 lire/life-year and ×1000 ptas/life-year, respectively.
†Costs are adjusted to reflect Spanish hospital admissions rates.
‡All 100 individuals in the cohort begin therapy in the described health state.
§The triple combination therapy (nevirapine/zidovudine/didanosine) is said to dominate the dual therapy (zidovudine/didanosine) because it costs less and provides improved survival.
‖Duration of effect is the number of months required for CD4 cell counts to return to baseline.
Incremental cost-effectiveness ratios are reported as local currency (LC) per life-year (LY) saved. All costs are reported in 1997 currency values.

effectiveness ratios become smaller as the discount rate increases. In the French, German, and Italian models, the incremental cost-effectiveness ratios become larger as the discount rate increases because the incremental survival declines at a slightly more rapid rate than incremental costs in these countries.

Discussion

This study, unlike those conducted during the past decade [10–17], estimates both the short- and long-term health benefits and economic performance of nevirapine triple therapy in five countries. The crossnational comparison, like that used by Simpson et al. [15] and Kempel et al. [11], captures country differences in epidemiological patterns, treatment practices, and reimbursement/regulatory strategies, providing decision-makers with the information critical to understanding the added value of nevirapine triple combination under different healthcare systems.

For each country, the models predict that nevirapine triple therapy provides superior health outcomes compared to ZDV/ddI dual therapy in the short term and is cost-effective in the long term. One hundred patients with a risk profile similar to those enrolled in the INCAS 1046 clinical trial may expect 34 fewer AIDS-related opportunistic disease events or deaths during the first year of therapy than patients treated with dual therapy. Examining the health benefits in the longer term suggests that overall survival would increase as well. Concomitantly, both short- and long-term budgetary implications arise as a result of the predicted improvement in health status.

In each of the five countries modeled, a sizeable proportion of the annual costs of nevirapine therapy (ranging from 60.9% to 142.1% after adjustment for baseline bias in the ACTG 241 clinical trial data) is offset by the expected savings in hospital care, medical visits, specialist consults, and medicines, all of which would be unnecessary given the predicted improvement in health status. Differences in treatment patterns (e.g., intensity and types of care provided) and medical care production costs affect the magnitude of the short-term medical care savings expected with the addition of an effective new therapy. As expected, these cost savings and cost-offsets are greater in healthcare systems that employ relatively more intensive types of care or where medical care production costs are higher (e.g., the United States) and lower in countries where treatment practices rely on less expensive types of care (e.g., Italy and Spain). A comparison of the net incremental cost (i.e., cost of the drug minus the expected cost savings) of adding nevirapine in each country reveals results similar to those of Anis et al. [17], who report net incremental costs ranging from Can $−2567 to Can$2648. Incremental costs for nevirapine therapy range (reported in 1996 Canadian dollars) from Can$−1201 (unadjusted Italian base case) to Can$2582 (unadjusted American base case). (1996 currency conversion rates: 1Can$ =

1.10 DM; 1Can$ = 3.75FF; 1Can$ = 92.87 ptas; 1Can$ = 1131.38 lire; 1Can$ = 0.73 US$.)

To place the results of the lifetime cost-effectiveness model into context, it is helpful to compare our incremental cost-effectiveness ratios with those reported for other types of HIV drug therapy. Early cost-effectiveness analyses of HIV monotherapies reported incremental cost-effectiveness ratios (in 1991 US$) ranging from US$6,553 to US$70,526 per life-year saved [13,43]. Studies of dual combination therapy [15,16] suggest ratios ranging from US$12,000 to US$20,000 per life-year saved. The study by Chancellor et al. [16], on which our long-term model is based, found an incremental cost-effectiveness ratio of US$10,311, or £6,276, for adding lamivudine to ZDV monotherapy. Most recently, Anis et al. [17] estimated that the first-year incremental cost-effectiveness ratios of adding a protease inhibitor to antiretroviral therapy might range from Can$10,481 to Can$98,074 per life-year gained (reported in 1996 Canadian dollars) or US$7,809 to US$73,067 (1997Can$ = 1.015859 1996Can$; 1 Can$ = 0.733389US$, 1996 average value). Cook et al. [46] report an incremental cost-effectiveness ratio of US$13,229 per life-year at 20 years for the addition of the protease inhibitor indinavir to dual combination therapy. Further, our results compare favorably to prophylaxis for Pneumocystis carinii pneumonia (US$16,000 per quality-adjusted life-year saved) [45] and with the thresholds promulgated by Laupacis et al. [47]. Even for the most sensitive parameter (i.e., time of therapy initiation), the incremental cost-effectiveness ratios for the five countries are only slightly higher than US$50,000 per life-year.

The reported results should be interpreted cautiously, recognizing that the models are based on current knowledge. As seen in the sensitivity analyses, the long-term model results were sensitive to the duration of the therapeutic effect of nevirapine. If triple therapy does not delay viral breakthrough as long as assumed in the models, then the models may overestimate the cost-effectiveness of nevirapine triple therapy. However, Montaner et al. [8] report that 69% of INCAS 1046 patients who were followed for more than 30 months (6 months longer than assumed in this model) had undetectable levels of virus. The model's base case assumption of nevirapine therapy duration likely is reasonable given current data. The estimated duration of protease inhibitor therapy and the assumption of declining effect for subsequent protease inhibitor therapy are based on the preliminary results of several studies [25,27–33]. Recently, Gulick et al. [26] reported that 66% of patients receiving indinavir, zidovudine, and lamivudine for 100 weeks had viral levels less than 50 copies/ml, suggesting that the duration of effect may be longer than that assumed in this model. The impact of uncertainties in the duration of effect for the protease combination probably would be distributed similarly between the dual and triple therapy arms, with little anticipated effect on the incremental cost-effectiveness ratio for nevirapine triple therapy.

The model results are those predicted for the addition of nevirapine to two particular nucleoside reverse transcriptase inhibitors, zidovudine and didanosine. The present comparators were selected on the basis of available clinical trial data; however, together they represent only one of the many possible combinations that can be used as part of the recommended therapy guidelines [4,5]. The preliminary results of two recent studies [48,49] indicate that nevirapine in combination with other nucleoside reverse transcriptase inhibitor dyads are as effective in reducing viral load as the combination used in this model. Therefore, repetition of these models with different therapy dyads likely would produce similar results.

Resource use data for the short-term model were derived from consensus panels composed of a small number of expert physicians from each of the five countries [12,15]. Although an attempt was made to achieve geographic representation, it is possible that other experts might specify different mixes of resource use and treatment patterns. Also, treatment patterns may have changed since the panels were conducted (1995–1996) and the mix of resources and the costs of care may be different now. If the country-specific care costs are less than those used in the model, the economic benefits of nevirapine triple therapy may be overestimated.

Also, Italian healthcare reform efforts made it difficult to obtain accurate costs in that country. Although the available DRG costs were employed in the model, many of the DRGs do not correspond directly to all the opportunistic disease events in the model, and in some cases, the DRGs include conditions that are not AIDS related. Thus, it is unclear whether the Italian DRGs reflect appropriate treatment patterns for the ODEs. The attempt to correct for the DRG resource mixtures by using Spanish hospital admissions patterns had relatively little effect on the results of either the short-or long-term models. As additional

cost and resource mix data become available in Italy, it may be prudent to reestimate these models.

Country-specific costs employed in the long term model were estimated by adjusting the health-state-specific costs from Chancellor et al. [16] using conversion rates derived from Simpson et al. [15] and Simpson and LaVallee [12]. The cost data in the Chancellor et al. [16] model represent the costs and treatment patterns within a single institution (Chelsea and Westminster Hospital in London) for a cohort of patients treated in 1994–1995. To the extent that treatment patterns have changed over time, the costs of care for opportunistic disease events may be different from those used.

The models do not specifically take into account the costs of adverse events associated with nevirapine or with the protease inhibitor combinations; these costs are assumed to be included in the health-state costs used. If side effects with nevirapine are much more costly than those of other combinations, then the costs of caring for these events may reduce the predicted medical care savings and cost offsets. To the extent that adverse events are similar and that their costs are small compared to the costs of providing care for opportunistic disease, these costs likely would have little effect on the incremental cost-effectiveness ratios. Finally, the value of earnings forgone as the result of HIV-related illness and premature death are excluded; only the costs of direct medical care are used in the models.

As the costs of HIV/AIDS care increase and resources become increasingly constrained, the decision to fund competing new therapy options will become more difficult. Government policy-makers and private payers will require information about the value for money of these therapies. Modeling, despite its limitations, can contribute to the needed information. The results of the present analysis provide administrators and decision-makers in the five countries some evidence that the added value of triple combination therapy with nevirapine, zidovudine, and didanosine falls within our expectations for cost-effective therapies in developed countries. They also support findings from previous studies [12,15] that the first-year cost-offset for a therapy depends on the cost structure of the care system. Further, this study demonstrates that it is possible to recycle well-constructed and documented cost-effectiveness models of antiretroviral therapy, and use them to gain insight into the factors that affect efficiency across countries and an understanding of the need to evaluate both short- and long-term economic forecasts when assessing antiretroviral therapies.

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